

(FILE 'MEDLINE, AGRICOLA, CANCERLIT, SCISEARCH, CAPLUS, EMBASE, BIOSIS, MEDICONF' ENTERED AT 18:17:48 ON 28 OCT 2002)

DEL HIS  
L1 129 S NEUROFILAMENT (L) SV40?  
L2 46 S L1 AND (NEURO? CELL)  
L3 16 DUP REM L2 (30 DUPLICATES REMOVED)  
L4 16 SORT L3 PY  
L5 549 S NEUROFILAMENT (L) PROMOTER  
L6 21 S L5 AND SV40?  
L7 9 DUP REM L6 (12 DUPLICATES REMOVED)  
L8 9 SORT L7 PY  
E RUDLAND PHILIP S?/AU  
L9 201 S E2  
L10 4 S E4  
L11 205 S L9 OR L10  
L12 132 DUP REM L11 (73 DUPLICATES REMOVED)  
L13 20 S L12 AND (NEURO? OR SV40? OR TGF? OR ERB? OR NF-L)  
L14 20 FOCUS L13 1-  
L15 4 S L13 AND TRANSGENIC

=> d an ti so au ab pi l15 3

L15 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

AN 1997:696860 CAPLUS

DN 127:355930

TI Conditionally immortalized cell lines derived from **transgenic** animals and their toxicological and pharmacological uses

SO PCT Int. Appl., 85 pp.

CODEN: PIXXD2

IN Rudland, Philip Spencer; Barraclough, Barry Roger; Kilty, Iain Charles; Davies, Barry Robert; Schmidt, Guenter

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AU 9725723	A1	19971107	AU 1997-25723	19970417
EP 904363	A1	19990331	EP 1997-917342	19970417
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JP 2000508897	T2	20000718	JP 1997-536877	19970417

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L14 20 FOCUS L13 1-

=> d an ti so au ab pi l14 1-6

L14 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2002 ACS

AN 1999:473378 CAPLUS

DN 131:284659

TI Development of hyperplasias, preneoplasias, and mammary tumors in MMTV-c-**erbB**-2 and MMTV-TGF.alpha. transgenic rats

SO American Journal of Pathology (1999), 155(1), 303-314

CODEN: AJPA44; ISSN: 0002-9440

AU Davies, Barry R.; Platt-Higgins, Angela M.; Schmidt, Gunter; Rudland, Philip S.

AB Human cDNAs corresponding to two epidermal growth factor-related products that are overexpressed in human breast cancers, that for c-**erbB**-2 (HER-2) and for transforming growth factor .alpha. (TGF .alpha.), have been cloned downstream of the mouse mammary tumor virus (MMTV) long terminal repeat promoter and injected into the pronucleus of fertilized oocytes of Sprague-Dawley rats to produce transgenic offspring. Expression of the transgenic mRNAs is not detectable in mammary tissue from virgin transgenic rats but is detected in mammary tissue from certain lines of mid-pregnant transgenic rats. When two such lines of either type of transgenic rat are subjected to repeated cycles of pregnancy and lactation, they produce, primarily in the mammary glands, extensive pathologies, whereas virgin transgenic rats produce no such abnormalities. Multiparous transgenic female offspring from c-**erbB**-2-expressing lines develop a variety of focal hyperplastic and benign lesions that resemble lesions commonly found in human breasts. These lesions include lobular and ductal hyperplasia, fibroadenoma, cystic expansions, and papillary adenomas. More malignant lesions, including ductal carcinoma in situ and carcinoma, also develop stochastically at low frequency. The mammary glands of transgenic females invariably fail to involute fully after lactation. Similar phenotypes are obsd. in female MMTV-TGF .alpha. transgenic rats. In addn., multiparous TGF .alpha.-expressing female transgenics frequently develop severe pregnancy-dependent lactating hyperplasias as well as residual lobules of hyperplastic secretory epithelium and genuine lactating adenomas after weaning. These transgenic rat models confirm the conclusions reached in transgenic mice that overexpression of the c-**erbB**-2 and TGF.alpha. genes predisposes the mammary gland to stochastic tumor development.

L14 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2002 ACS

AN 1998:301412 CAPLUS

DN 129:107334

TI Cytoplasmic staining of c-**erbB**-2 is not associated with the presence of detectable c-**erbB**-2 mRNA in breast cancer specimens

SO International Journal of Cancer (1998), 76(4), 459-463

CODEN: IJCNAW; ISSN: 0020-7136

AU Taylor, Susan L.; Platt-Higgins, Angela; Rudland, Philip S.; Winstanley, John H. R.; Barraclough, Roger

AB The cell-surface receptor tyrosine kinase protein c-**erbB**-2 is

immunocytochem. detected as membrane staining on the surface of cancer cells in 20-30% of cases of breast cancer, and its presence has been assocd. with poor prognosis for the patient. However, there have been numerous reports of immunocytochem. staining for c-erbB-2 solely in the cytoplasm of some normal and tumor specimens with frequently used anti-sera, and the presence of such staining has been difficult to interpret. It is not known for certain that cytoplasmic c-erbB-2 staining is an artifact of the immunocytochem. procedures used. Thus, mRNA for c-erbB-2 has been quantified in tumors exhibiting only cytoplasmic staining or varying levels of membrane staining using a sensitive, competitive PCR method. Whereas abundant levels of c-erbB-2 mRNA are found in tumors exhibiting membrane staining for c-erbB-2 and these levels correlate with the percentage of tumor cells showing membranous staining for c-erbB-2, the level of c-erbB-2 mRNA in tumors displaying only cytoplasmic staining is no higher than in c-erbB-2-neg. specimens.

L14 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2002 ACS

AN 2000:517394 CAPLUS

DN 134:3315

TI c-erbB-2 mRNA in breast cancer specimens that exhibit membrane or cytoplasmic immunoreactivity for c-erbB-2

SO Oncology Research (1999), 11(7), 311-317

CODEN: ONREE8; ISSN: 0965-0407

AU Taylor, Sue L.; Rudland, Philip S.; Barraclough, Roger

AB Immunocytochem. detected membrane staining for c-erbB-2 in 20-30% of breast cancers correlates with a poorer prognosis for the patients. However, cytoplasmic immunoreactivity for c-erbB-2 has also been found in some specimens using some particular antisera, and it has been suggested that this staining arises from a protein located in the mitochondrial membrane. It is possible that this protein is an alternative form of c-erbB-2. In the present article, adjacent histol. sections have been stained for c-erbB-2 immunocytochem., and for c-erbB-2 mRNA by in situ hybridization. The results show the absence of c-erbB-2 mRNA in regions of cancer specimens that exhibit cytoplasmic staining for c-erbB-2, strongly suggesting that cytoplasmic staining for c-erbB-2 is an immunocytochem. artifact.

L14 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2002 ACS

AN 1998:9289 CAPLUS

DN 128:73597

TI Induction of a variety of preneoplasias and tumors in the mammary glands of transgenic rats

SO Biochemical Society Symposia (1998), 63(Mammary Development and Cancer), 167-184

CODEN: BSSYAT; ISSN: 0067-8694

AU Davies, Barry R.; Warren, Joe R.; Schmidt, Gunter; Rudland, Philip S.

AB Although transgenic mouse models for breast cancer have frequently been reported in the literature, transgenic rat models have not been described. The authors have generated transgenic rats overexpressing the human transforming growth factor .alpha. (TGF.alpha.) and c-erbB-2 genes in the mammary gland under the control of the mouse mammary tumor virus (MMTV) long terminal repeat promoter, and have analyzed multiple lines of these rats to the second (F2) generation. Female MMTV/TGF.alpha. rats frequently develop severe hyperplasias during pregnancy, and a variety of tumors of long latency. The mammary glands of MMTV/TGF.alpha. rats fail to involute fully after the completion of lactation. Expression of the TGF.alpha. transgene is highest in the hyperplasias. MMTV/c-erbB-2 female rats develop a spectrum of benign and malignant lesions, including ductal carcinoma in situ and carcinomas. Expression of the c-erbB-2 transgene is found in benign tumors such as fibroadenomas, but is highest in the carcinomas. These animals model a spectrum of lesions found in human breasts and suggest that TGF.alpha. overexpression can act at a relatively early stage in the pathogenesis of breast cancer in the rat, resulting in a predominantly hyperplastic response, whereas overexpression of c-erbB-2 plays a role in the induction of various benign lesions and more advanced breast carcinomas.

L14 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2002 ACS  
 AN 1997:696860 CAPLUS  
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SO PCT Int. Appl., 85 pp.  
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JP 2000508897	T2	20000718	JP 1997-536877	19970417

L4 ANSWER 6 OF 16 MEDLINE  
AN 95120525 MEDLINE  
TI Conditional immortalization of **neuronal cells** from postmitotic cultures and adult CNS.  
SO BRAIN RESEARCH, (1994 Sep 12) 656 (2) 396-404.  
Journal code: 0045503. ISSN: 0006-8993.  
AU Eves E M; Kwon J; Downen M; Tucker M S; Wainer B H; Rosner M R  
AB To determine whether postmitotic neurons can be immortalized by oncogenic transduction, we used two approaches involving conditional expression of a temperature-sensitive **SV40** large T antigen (Tts). Initially, Tts was introduced into E17 rat embryonal hippocampal cells that were then cultured at the non-permissive temperature to enrich for postmitotic pyramidal neurons, and subsequently cloned at the permissive temperature. One clonal line (HMR10-3) expressed neuron-specific proteins upon differentiation, was capable of generating action potentials, and formed synapses with primary rat neurons in co-culture. Replating of these

postmitotic cells at the permissive temperature resulted in reversible loss of **neurofilament** expression. Conditionally immortalized cell lines were also generated from the brain of an adult mouse carrying an inducible Tts transgene. These lines proliferated in a T antigen-dependent manner and expressed neuron-specific proteins upon differentiation at the non-permissive temperature. These results suggest that postmitotic neurons can be induced to enter the cell cycle without losing their commitment to a neuronal lineage.

- L4 ANSWER 7 OF 16 MEDLINE  
 AN 95054390 MEDLINE  
 TI Distinct regulatory pathways control neurofilament expression and neurotransmitter synthesis in immortalized serotonergic neurons.  
 SO JOURNAL OF NEUROSCIENCE, (1994 Nov) 14 (11 Pt 1) 6744-53.  
 Journal code: 8102140. ISSN: 0270-6474.  
 AU White L A; Eaton M J; Castro M C; Klose K J; Globus M Y; Shaw G; Whittemore S R  
 AB Following infection of dissociated embryonic day 13 rat medullary raphe cells with a retrovirus encoding the temperature-sensitive mutant of **SV40** large T-antigen (T-ag), a **neuronal cell** line, RN46A, was cloned by serial dilution. At 33 degrees C, RN46A cells express nuclear T-ag immunoreactivity and divide with a doubling time of 9 hr. Undifferentiated RN46A cells express low levels of neuron-specific enolase (NSE) and low (NF-L)- and medium (NF-M)- but not high (NF-H)-molecular-weight **neurofilament** proteins. Under differentiation conditions, RN46A cells cease dividing, take on a neuronal morphology, and express enhanced levels of NSE and all three NF proteins. Elevation of intracellular cAMP levels increases **neurofilament** protein expression, whereas activators of various other intracellular second messenger systems have no effect. Differentiated RN46A cells express low-affinity nerve growth factor (NGF) receptor (p75NGFR) and are immunoreactive using an antibody that recognizes the carboxy-terminal 13 amino acids of all three trk proteins (pan-trk). Both immunoreactivities could be potentiated by treatment with brain-derived neurotrophic factor (BDNF), NGF, and adrenocorticotrophic hormone, fragment 4-10 (ACTH4-10). Differentiated RN46A cells express low levels of tryptophan hydroxylase (TPH) immunoreactivity, which could be enhanced by treatment with ACTH4-10, BDNF, or NGF. Low levels of serotonin immunoreactivity are detected in differentiated RN46A cells, and this was potentiated by differentiating RN46A cells with BDNF for 8 d and 40 mM KCl for days 4-8. HPLC analysis confirmed these immunohistochemical data. RN46A cells should prove useful to elucidate intracellular mechanisms that control **neurofilament** assembly and 5-HT expression in differentiating raphe neurons.
- L4 ANSWER 13 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.  
 AN 97240795 EMBASE  
 TI Immortalization of neuro-endocrine cells from adrenal tumors arising in SV40 T-transgenic mice.  
 SO Oncogene, (1997) 14/25 (3093-3098).  
 Refs: 40  
 ISSN: 0950-9232 CODEN: ONCNES  
 AU Cairns L.A.; Crotta S.; Minuzzo M.; Ricciardi-Castagnoli P.; Pozzi L.; Ottolenghi S.  
 AB Pheochromocytomas are adrenal medullary tumors which arise from the transformation of neural crest-derived cells. In the course of studies of mice transgenic for an **SV40** T-gene ectopically expressed in the adrenal medulla, we observed the occurrence of large, mainly bilateral tumors in a high proportion of transgenic animals. From these tumors we established immortalized cell lines which grow in vitro at 32.degree.C (the permissive temperature for the tsA58 T-protein encoded by the transgene), but not at 38.degree.C. These cells demonstrate characteristics of both neuronal (160 kd **neurofilament**) and endocrine (chromogranins) cells. The expression of Mash-1 and ret supports their initial characterization as early bipotential neuro-endocrine progenitors.

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JP 2000508897 T2 20000718 JP 1997-536877 19970417

L8 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2002 ACS

AN 2000:412036 CAPLUS

DN 133:27367

TI Transgenic animals expressing a reporter gene in specific cellular locations useful for drug screening

SO Jpn. Kokai Tokkyo Koho, 20 pp.

CODEN: JKXXAF

IN Kaisei, Yoshihiko; Kasuga, Hisao

AB Recombinant expression vector for the prepn. of transgenic animal, e.g. mouse, carrying a reporter gene .beta.-galactosidase under the control of the **neurofilament** light chain **promoter**, and either

growth annexing protein 43 gene axon targeting signal sequence or SV40 nuclear translocation signal sequence, is disclosed. Transgenic animals transformed with such a vector and expressing a reporter gene in specific cellular locations, eg. subcellular organelles, is also claimed. A method of screening for compds. useful for prevention and therapy for cell degeneration is also claimed. Preventive and therapeutic agents for central nervous system disorders, mental disorders, kidney diseases, bone diseases, joint diseases, lung diseases, arteriosclerosis, heart diseases, digestive system disease, infectious diseases, allergic diseases, endocrine diseases, dementia, and cancer are claimed.

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PI	JP 2000166575	A2	20000620	JP 1999-276566	19990929

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